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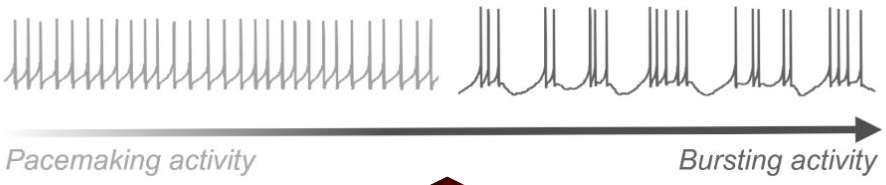

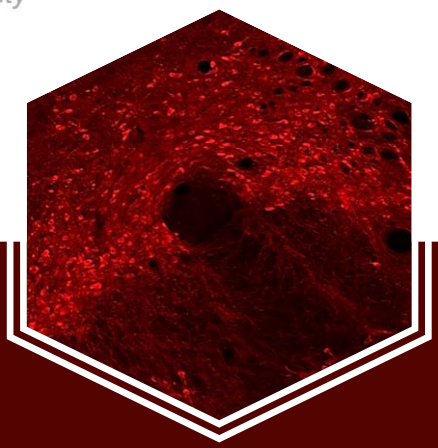

SOFIAN RINGLET

Thesis presented for the purpose of obtaining the degree of
Doctor in Biomedical and Pharmaceutical Sciences

Supervisor: Dr. Dominique Engel

UNIVERSITY OF LIEGE
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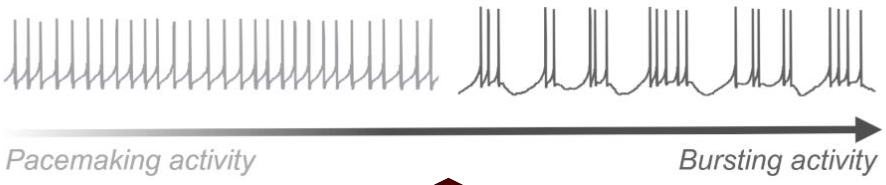

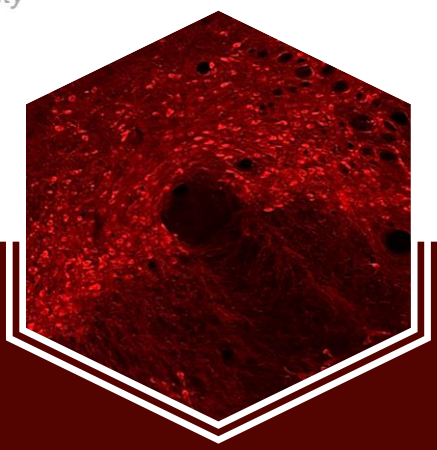

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ABSTRACT

Dopamine neurons of the substantia nigra pars compacta are central components of the basal ganglia circuitry and play a fundamental role in the initiation, selection, and execution of voluntary movements. Their activity exhibits distinct firing modes, ranging from regular pacemaking to high-frequency burst firing. These firing patterns constitute meaningful neural codes that shape dopamine release in downstream target regions. In particular, burst firing produces transient elevations in extracellular dopamine levels and is temporally associated with movement initiation and the encoding of salient motor-related signals. Despite its importance, the cellular and synaptic mechanisms governing the transition from pacemaking to burst firing remain incompletely understood. Burst firing in dopamine neurons critically depends on the activation of N-methyl-D-aspartate receptors, a class of glutamate-gated ion channels with unique activation requirements. In addition to glutamate binding, N-methyl-D-aspartate receptors require the simultaneous binding of a co-agonist at a distinct modulatory site, typically occupied by either glycine or D-serine, for channel opening. The availability and spatial distribution of these co-agonists therefore constitute key regulatory elements of N-methyl-D-aspartate receptor function. However, how co-agonist signalling interacts with synaptic versus extrasynaptic receptor populations to control burst firing remains poorly understood.

Using *ex vivo* electrophysiological recordings from adolescent rats, this thesis demonstrates that extrasynaptic N-methyl-D-aspartate receptors are the primary drivers of burst firing in dopamine neurons of the substantia nigra pars compacta. We show that these receptors are preferentially recruited during periods of intense synaptic activity through glutamate spillover beyond the synaptic cleft. Full activation of extrasynaptic N-methyl-D-aspartate receptors critically requires the binding of the co-agonist glycine. In contrast, basal synaptic transmission, which predominantly engages synaptic N-methyl-D-aspartate receptors supported by D-serine, is insufficient to trigger burst firing. Importantly, synaptic and extrasynaptic N-methyl-D-aspartate receptors share an identical subunit composition, indicating that differences in molecular identity do not underlie their distinct functional contributions. Instead, burst generation seems to be governed by the spatial localisation of N-

methyl-D-aspartate receptors and by the regionalized availability of their co-agonists within the extracellular space. These findings reveal a previously underappreciated mechanism by which glutamate spillover and co-agonist compartmentalisation regulate the firing mode of dopamine neurons.

Together, this work identifies receptor localisation and co-agonist regulation, rather than receptor subunit composition, as key determinants of burst firing in dopamine neurons. By defining the glycine-dependent, extrasynaptic mechanisms that govern burst generation, this thesis provides a comprehensive framework for understanding how dopamine neurons encode movement-related signals and refines current models of the physiological role of dopamine in motor control.

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